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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RUTH A. GIERSET
and ROBERT E. SOBOL

Appeal No. 1999-1306
Application No. 08/335,461

HEARD: October 23, 2001

Before WINTERS, ROBINSON, and MILLS, Administrative Patent Judges.

ROBINSON, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 2, 4 - 20, and 23, which are all of the claims pending in this application.

Claims 1 and 2 are illustrative of the claims on appeal and read as follows:

1. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:

delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and

subjecting said tumor cell to said cancer therapy.

2. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:

delivering a wild-type p53 protein to a tumor cell which is deficient in its wild-type p53 gene, and

subjecting said tumor cell to said cancer therapy.

The references relied on by the examiner are listed below:

Wu et al. (Wu)	5,166,320	Nov. 24, 1992
Srivastava	5,252,479	Oct. 12, 1993
Nabel et al. (Nabel)	5,328,470	Jul. 12, 1994
Eppstein et al. (Eppstein)	5,366,737	Nov. 22, 1994

Malkin et al. (Malkin), "Germ Line p53 Mutations in a Familial Syndrome of Breast Cancer, Sarcomas, and Other Neoplasms," Science, Vol. 250, pp, 1233-1238 (1990)

Chen et al. (Chen), "Expression of wild-type p53 in human A673 cells suppresses tumorigenicity but not growth rate," Oncogene, Vol. 6, pp. 1799-1805 (1991)

Cheng et al. (Cheng), "Suppression of Acute Lymphoblastic Leukemia by the Human Wild-Type p53 Gene," Cancer Research, Vol. 52, pp. 222-226 (1992)

Moossa et al. (Moossa), Comprehensive Textbook of Oncology, Williams & Wilkins, Baltimore, Md., Vol. 1, pp. 477, 527-536, 565-568, 590-594, 607-612, Vol. 2, pp. 1098, 1138-1140, 1170, 1329, 1368, and 1569-1572, (1991)

The three references relied on by the appellants are listed below:

Vogelstein et al. (Vogelstein), "p53 Function and Dysfunction," Cell, Vol. 70, pp. 523-526 (1992)

Shimizu et al. (Shimizu), "RB protein status and clinical correlation from 171 cell lines representing lung cancer, extrapulmonary small cell carcinoma, and mesothelioma," Oncogene, Vol. 9, pp. 2441-2448 (1994)

Stone et al. (Stone), "Reversible, p16-mediated Cell Cycle Arrest as Protection from Chemotherapy," Cancer Research, Vol. 56, pp. 3199-3202 (1996)

Grounds of Rejection

Claims 1, 2, 4 - 11, and 17 - 20 stand rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Cheng, Srivastava, and Moossa.

Claims 12 - 18 and 20 stand rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Cheng, Srivastava, Moossa, Wu, Malkin, and Chen.

Claims 1, 2, 4 - 15, and 17 - 20 stand rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Nabel, Wu, Malkin, and Moossa.

Claim 23 stands rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Cheng, Srivastava, Moossa, and Eppstein.

Claim 23 stands rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Nabel, Wu, Malkin, Moossa, and Eppstein.

We reverse these rejections for the reasons set forth herein.

Claim interpretation

Claim 1 is directed to a method of increasing the therapeutic effect of a cancer therapy comprising the steps of delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said cell and subjecting the tumor cell to said cancer therapy. Appellants have

argued in their Appeal Brief (Brief) at page 3 and at the oral hearing that the claim should be read as a method of sensitizing a tumor cell to the effect of the subsequently applied cancer therapy. The specification would reasonably appear to support this interpretation at page 3 where it states "The method includes introducing into tumor cells a source of wild-type therapy-sensitizing gene activity and subjecting the cells to a cancer therapy" and at page 4 where it states "[b]y 'therapy-sensitizing gene' activity is meant a gene or gene product whose loss of normal function or regulation renders cancer cells more resistant to therapy. Restoration of therapy-sensitizing gene function results in increased sensitivity of cancer cells to therapy." The appellants, additionally, urge (Reply Brief, pages 2-3), and we concur, that claim 1 does not encompass increasing the therapeutic effect of the cancer treatment in the patient in general, but is limited to sensitizing the effect of the subsequently applied cancer treatment to the tumor cell which has been transformed with the wild-type p53 gene where expression of that gene has been effected. Thus, we do not read claim 1 as encompassing the treatment of non-altered or non-transformed tumor cells with a cancer therapy or the general treatment of a cancer patient in this manner.

Claim 2 differs from claim 1 in providing that a wild-type p53 protein is delivered to a tumor cell rather than a wild-type p53 gene which is subsequently expressed. In briefing the issues raised by this appeal, neither the examiner nor appellants have separately addressed the methodology of claim 2 to the extent that it might differ from claim 1. Since the appeal is presented to us in this form and appellants have indicated

that all claims are to be considered in one group (Brief, page 6), we will consider the issues raised on this record as they are directed to the methodology of claim 1 as representative of the claims on appeal. 37 CFR § 1.192(c)(7)(1996).

Discussion

The rejections under 35 U.S.C. § 103

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant. Id. In order to meet that burden the examiner must provide a reason, based on the prior art, or knowledge generally available in the art as to why it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297, n.24, 227 USPQ 657, 667, n.24 (Fed. Cir.), cert. denied, 475 U.S. 1017 (1986).

In rejecting the claims on appeal under 35 U.S.C. § 103 the examiner, initially, relies on Cheng as describing (Answer, page 5):

> suppression of T-cell acute lymphoblastic leukemia (T-ALL) post transfection of T-ALL cells with a vector effecting expression of the p53 gene product (see at least the abstract). The reference indicated therapeutic treatment suppressed unregulated growth of T-ALL cells by introduction of the DNA encoding p53 into cells in conjunction with autologous bone marrow transplantation regimes in an effort to reduce the frequency of posttransplantation relapse.

Similarly, in a separate ground of rejection under 35 U.S.C. § 103 the examiner relies on Nabel as disclosing (Answer, page 7):

> genetic therapy by transforming cells in vivo to treat malignancies (col 11-12) by inhibiting tumor cell growth by gene transfer directly into the tumor cells where (1) the transforming DNA induced rejection, regression or both of the tumor (col 12, lines 45+); (2) the vector is a liposome complex and/or conjugated with for example polylysine (col 11, line 15+ and col 14, line 60+) . . . .

The examiner relies on Srivastava and Wu as providing the methodology and means by which the DNA required by both Cheng and Nabel may be delivered to the tumor cell (Answer, pages 5 and 6). The examiner relies on Moossa as describing the known methods of treatment of cancer and/or tumors which have been successfully used and to demonstrate that these treatments "are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations." (Answer, page 6).

The examiner concludes that (Answer, page 6):

> [t]he combined references would have resulted in the claimed process wherein a DNA (i.e., the gene encoding a wild-type p53) encoding a tumor sensitizing product was delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers.

The examiner expands on these statements in responding to appellants' arguments, stating (Answer, paragraph bridging pages 11-12):

> combinatorial therapies are known and clinically practiced and it would have been obvious to one of ordinary skill in the art to have (1) used known vectors and processes demonstrated as effective that are known to

> function in vivo for delivery of known DNA encoding wild-type p53 for which the Srivastava reference disclosed vectors are safe for gene therapy . . . Moreover, where the Cheng et al. reference referred to bone marrow transplantation regimes it would have been obvious to any one of ordinary skill in the art that radiation therapy . . , chemotherapy . . , biological therapy . . , cryotherapy . . , and hyperthermia . . . are known treatment methods, have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent . . .

Thus, as we understand the examiner's premise, Cheng and Nabel establish that the transformation of a tumor cells with the DNA which encodes wild-type p53 and is expressible therein for the purpose of suppressing the growth of the tumor was known in the prior art. Srivastava and Wu provides the means and methodology of delivering this DNA to the tumor cells as well as the means of obtaining expression in order to provide the wild-type p53 protein to the cell. Moossa establishes that the use of the various therapies such as chemotherapy and radiation therapy, in combination are also known. Thus, it would have been obvious within the meaning of 35 U.S.C. § 103 to use the methodology provided by either Cheng or Nabel in combination with those other known and recognized treatments of cancer and/or tumors.

Appellants do not dispute the teachings of the individual references but do urge that there is no suggestion or incentive to combine the teachings of these references in a manner which would have led to the presently claimed invention. (Brief, page 20). Appellants urge that (Brief, page 21):

> [t]he references cited in the Final Office Action each described a part of the claimed process but they did not describe the whole process or suggest combining the parts to make the whole process.

We agree that there is no explicit statement or suggestion to treat a tumor cell by delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of this gene in the tumor cell and then subjecting the tumor cell to cancer therapy as presently claimed. However, such an explicit teaching is not essential to establish a prima facie case of obviousness within the meaning of 35 U.S.C. § 103. The references may reasonably be relied upon for all that they would have reasonably suggested to one having ordinary skill in the art. Merck & Co. v. Biocraft Lab., Inc., 874 F.2d 804, 808, 10 USPQ2d 1843, 1846 (Fed. Cir), cert. denied, 493 U.S. 975 (1989); In re Lamberti, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976). Here, the examiner's rejections reasonably appear to be based on the premise that those of ordinary skill in this art would recognize, as they have in the past, the benefit to be derived from the use of a combination of therapies in the treatment of cancer and/or tumors. Moossa provides evidence which would reasonably support this proposition.

Thus, the examiner urges that (Answer, page 13):

> the therapy using p53 in combination with conventional therapies is expected to have the same effect as disclosed in the references and the conventional therapies used with the gene therapy for p53 is expected as for example disclosed in the Moossa et al. reference is expected to [have] the same effect as when used alone. Thus, each form of therapy is expected to have its own addition to the effect of the therapy and each together is expected to at least have an additive effect. The additive

> effect is an increased therapeutic effect over each of the therapies alone. . . Thus, in either instance, the combinatorial therapy is expected to produce an increased therapeutic effect.

The difficulty arises when one tries to predict what that additive effect would be. Cheng describes the ability of the use of wild-type p53 therapy as "suppressing the tumorigenicity of human . . . cells", while Nabel only mentions p53 therapy in general terms. Thus, neither Cheng or Nabel can be said to describe the use of therapy involving wild-type p53 DNA as a means of killing or destroying tumor cells. On the other hand, as the examiner (Answer, 13) and appellants (Brief, page 23) both recognize, the type of cancer treatments described by Moossa are directed to the intended purpose of killing or eliminating tumor cells. Thus, it is not readily apparent what type of additive effective one would expect were the two therapies used in combination.

In this regard, appellants, additionally, argue that (Brief, page 23):

> the expression of wild-type p53 gene in tumor cells would be expected to reduce, rather than increase the sensitivity of the tumor cells to chemotherapy and radiation because wild-type p53 gene suppresses tumor cell growth.

In support of this proposition, appellants have submitted the article by Vogelstein which is urged to suggest that the absence of wild-type p53, as represented by the presence of p53 mutations would increase sensitivity to antitumor agents, and by analogy suggests that the presence of wild-type p53 would have been expected to decrease sensitivity to antitumor agents. (Brief, page 23). Similarly, appellants have

provided articles by Shimizu and Stone[1] (Reply Brief, pages 4-5) which describe the resistance to cisplatin and other chemotherapeutic agents which resulted when the tumor suppressor gene wild-type Rb and wild-type p16 gene are transfected into tumor cells. While the examiner has dismissed the evidentiary value of these two references as not relating to wild-type p53 expression in tumor cells (Supplemental Examiner's Answer, page 3), it remains that these three articles are the only substantive evidence of record which would speak to what benefit one of ordinary skill in the art would have expected from the use of the suppressor gene which expresses wild-type p53 in combination with other cancer therapies.

Thus, appellants have provided evidence which would reasonably suggest that one of ordinary skill in this art at the time of the invention would have expected that the likely result of combining the therapies of Cheng and Nabel with the other types of cancer therapies described by Moossa would have been that the transformed tumor cells would have been more resistant to such cancer therapies. This is consistent with the examiner's analysis that (Answer, page 19):

> the cells expressing wild-type p53 have suppressed tumor cell phenotype which effectively [resulted in] a "normal" cell phenotype. Cancer therapy is not directed to killing "normal" cells,

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[1] We recognize that Stone was published subsequent to the filing of this application and therefore may not demonstrate the state of the art at the time of the invention by appellants. However, it does support the disclosure provided by the other two articles cited by appellants and would reasonably appear to suggest that even two years after the filing of the present application, the insertion and expression of the suppressor gene for wild-type P16 was observed to have the effect on transformed cells of desensitizing those cells to subsequent treatment.

The examiner, additionally, urges that (id.):

> where not all cancer cells are effectively transformed, the remaining cancer cells with no heterologous genetic material are more easily treated due to sensitivity to known clinical regimens.

However, appealed claim 1, as we have interpreted it, is not directed to the treatment of non-transformed tumor cells or to cancer patients in general and therefore this type of treatment would not fall within the scope of the claims before us.

Given the unpredictability associated with both gene therapy and cancer therapy and the fact that these two types of therapy reasonably appear to differ significantly as to mechanism of action and results expected, it would be difficult to predict just what type of results would be expected from the use of this combination of therapies. In addition, the evidence would suggest that one of ordinary skill might well expect that, rather than an additive or beneficial result, a desensitizing of the tumor cells to the other forms of cancer therapy could result. Thus, it would reasonably appear that while it might be obvious to try to treat tumor cells with a combination of delivering a wild-type 53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell and subjecting said tumor cell to said cancer therapy, it can not be said that the expected results could have been easily defined. While absolute predictability is not required, a reasonable expectation of success is needed to support a conclusion of obviousness. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); In re Longi, 759 F.2d 887, 897,

225 USPQ2d 645, 651-52 (Fed. Cir. 1985). The record before us does not provide that reasonable expectation of success.

Thus, when we consider the claimed subject matter as a whole and the facts and evidence provided by the examiner and weigh these facts and evidence against the facts and evidence presented by appellants, we find that, on balance, the evidence in favor of the non-obviousness of the claimed subject matter out weighs the evidence in favor of obviousness.

Therefore, we reverse the rejection of claims 1, 2, 4 - 11 and 17 - 20 as unpatentable over Cheng, Srivastava, and Moossa, and the rejection of claims 1, 2, 4 - 15, and 17 - 20 as unpatentable over Nabel, Wu, Malkin, and Moossa.

To the extent that the examiner has maintained the separate rejection of claims 12 - 18 and 20 as unpatentable over Cheng, Srivastava, Moossa, Wu, Malkin and Chen, it is sufficient to note that Wu, Malkin and Chen do not provide that which we have determined to be missing from the combined teachings of Cheng, Srivastava and Moossa. Similarly, Eppstein, which is additionally relied on in the rejections of claim 23, does not provide that which has been determined to be missing from the remaining references. Therefore, we, additionally, reverse the rejections of claims 12 - 18, 20, and claim 23.

Other Issues

At the oral hearing held October 23, 2001, appellants' representative provided a copy of U. S. Patent 6,069,134 which issued, subsequent to the briefing of this appeal

by both the examiner and appellants, on May 30, 2000 from Application No. 08/953,290, filed October 17, 1997. A copy of this patent has now been made a part of the record in this case. We note that, like the application on appeal, the application which resulted in this U. S. Patent includes a prosecution history involving a series of continuation-in-part applications. The subject matter to which this patent is directed readily appears to correspond to a significant degree with the subject matter before us on appeal. Compare claim 1 of the patent with appealed claim 1. We leave it to the examiner, in the first instance, to review this patent, and the prosecution history thereof, to determine the effective filing date of each claim therein. The examiner should do the same with the claims of this application. Only at that point will it be appropriate to determine 1) whether the patent constitutes prior art within the meaning of 35 U.S.C. § 102(e) or 2) whether an interference proceeding is appropriate between the patent and the present application. Should the examiner determine that further prosecution is appropriate, that determination should be communicated to the applicants and they should be provided an appropriate opportunity to respond thereto.

Appeal No. 1999-1306
Application No. 08/335,461

SUMMARY

The rejections of appealed claims 1, 2, 4 - 20, and 23 under 35 U.S.C. § 103 are reversed.

REVERSED

SHERMAN D. WINTERS
Administrative Patent Judge

DOUGLAS W. ROBINSON
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

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